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Supporting Information

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Primary Peptide Folding Dynamics Observed with Ultrafast *T*-Jump

Omar F. Mohammed,[1] Gouri S. Jas,[2] Milo M. Lin,[1] and Ahmed H. Zewail[1]*

[1]*Physical Biology Center for Ultrafast Science and Technology, Arthur Amos Noyes Laboratory of Chemical Physics, California Institute of Technology, Pasadena, CA 91125, USA*

[2]*Department of Chemistry, Biochemistry, and Institute of Biomedical Studies, Room: C322 Baylor University, 101 Bagby Avenue, Waco, TX 76706, USA*

Received:

*Fax: (626) 792-8456; E-mail: zewail@caltech.edu

Materials

The peptides Ac-W$(A)_3H^+$-NH_2 (Wh5) and 21-residue helical heteropeptide (Ac-W$AAAH^+(AAARA)_3$A-NH_2) (Wh21) were obtained from California Peptide Research with > 98% purity. Peptide concentrations were determined from the optical absorbance at 280 nm, using molar extinction coefficients of 5690 $M^{-1}cm^{-1}$. Solutions were buffered with 20 mM sodium acetate at pH = 4.8. The final sample concentrations for the circular dichroism and kinetic measurements were 0.35 mM.

Equilibrium Experiments

Natural circular dichroism was measured with a Jasco 810 spectropolarimeter at a peptide concentration of 350 μM with 0.05 cm pathlength cyllindrical cuvette. Tryptophan fluorescence at 300–450 nm was measured with a Spex Fluorolog spectrofluorimeter, using 30 μM peptide samples excited at 280 nm with minimal exposure of sample to the excitation light to avoid photodamage.

***T*-jump Method**

The detailed experimental procedure for an ultrafast laser temperature jump setup has been described elsewhere.[1] Here, we briefly present some modifications. The near- IR signal and idler pulses were generated by two optical parametric amplifier (OPA) systems pumped by a Ti: sapphire amplifier laser system operating at 800 nm (Spectra-Physics) with a repetition rate of 200 Hz. The *T*-jump pulse was set to 1.45 μm with a sufficient energy, typically 15-20 μJ at the sample. This frequency of the *T*-jump corresponds to the weak overtone of the OH stretch vibration of H_2O. The probe pulse tuned at 280 nm was generated by a two-step frequency conversion: first the visible pulse tuned at 580 nm is generated by sum frequency mixing of the fundamental laser output (800 nm) with the idler of OPA, tuned to 1870 nm. Second, the generated visible pulse (560 nm) is frequency-doubled in a BBO crystal. The probe pulse has much less energy (< 1 nJ). The sample solutions were enclosed in a 100 μm thick flat capillary tube placed in a thermally jacketed temperature controller (LakeShore) to carefully monitor the initial temperatures.

MD Simulations

The all-atom CHARMM22/CMAP force field was used for all calculations.[2, 3] In addition to the polypeptide, 872 TIP3P water molecules and one chloride ion were added as a 61.5 mM salinity solvent yielding an electrically neutral system comprising 2698 atoms.The 100 starting structures for each independent trajectory was randomly selected from the equilibrated ensemble at 311 K. This ensemble consists of the structures from a single 20 ns MD trajectory at 311 K starting from a random structure.

References

[1] H. R. Ma, C. Z. Wan, A. H. Zewail, *J. Am. Chem. Soc.* **2006**, *128*, 6338.

[2] A. D. B. MacKerell, D. Bellott, M. Dunbrack, R. L. Evanseck, J. D. Field, M. J. Fischer, S. Gao, J.Guo, H.Ha, S.Joseph-McCarthy, D.Kuchnir, L.Kuczera, K. Lau, F. T. K. Mattos, C. Michnick, S. Ngo, T. Nguyen, D. T. Prodhom, B. Reiher, W. E. Roux, B. Schlenkrich, M. Smith, J. C. Stote, R. Straub, J., M. W.-K. Watanabe, J. Yin, D. Karplus, M., *J. Phys. Chem. B* **1998**, *102*, 3586.

[3] A. D. MacKerell, M. Feig, C. L. Brooks, *J. Am. Chem. Soc.* **2004**, *126*, 698.

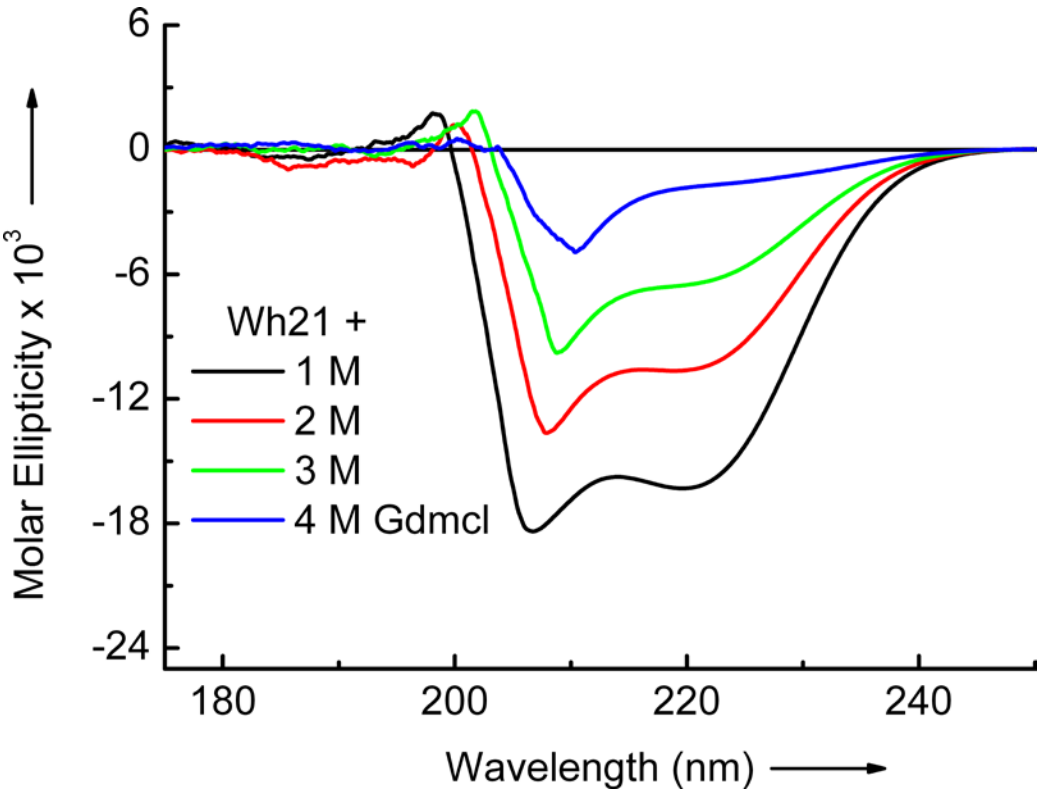

Figure S1: The CD spectra (molar ellipticity / deg cm^2 $dmole^{-1}$) of Wh21 with varying Gdmcl concentrations in acetate buffer (pH = 4.8) at 300 K, showing minima similar to the Wh5 peptide at higher denaturing levels.

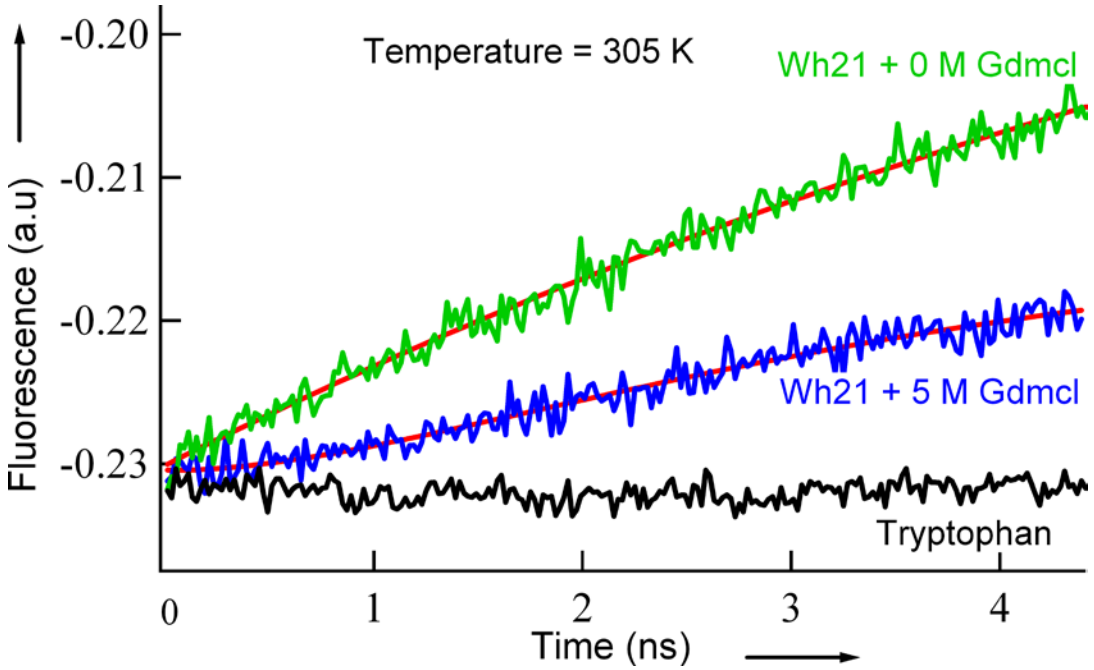

Figure S2: Transient evolution of the tryptophan fluorescence of peptide model Wh21 in acetate buffer at pH = 4.8 with 0 M Gdmcl (green) and with 5 M Gdmcl (blue) following ultrafast laser-induced *T*-jump at 305 K final temperature. The flat black curve is the fluorescence of the free tryptophan in water under identical conditions following *T*-jump, which is used as reference.

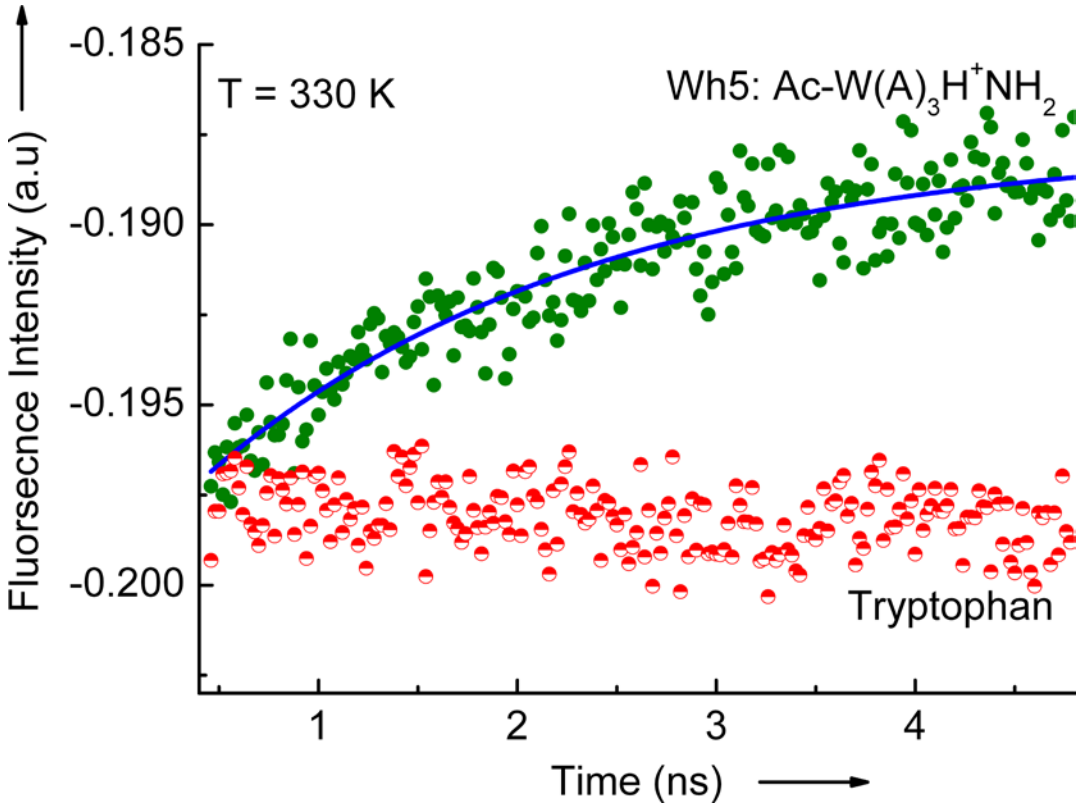

Figure S3: Transient evolution of peptide following *T*-jump. Shown are the tryptophan fluorescence of Wh5 (20 mM acetate buffer at pH = 4.8) in response to the *T*-jump for final temperatures of 330 K. The dynamics is finished within the time window of 4.8 ns.